GlaxoWellcome

August 31, 1999

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

Re: Draft Guidance for Industry: Establishing Pregnancy Registries; Docket No. 99D-1541; *Federal Register* 64: 30041 (June 4, 1999); Comments for Consideration

Dear Sir or Madam:

Reference is made to FDA's issuance of a draft guidance for industry on establishing pregnancy registries (*Federal Register* 64: 30041 [June 4, 19991). This notice requested that all interested persons submit written comments to FDA by September 2, 1999. The purpose of this letter is to provide comments on this draft guidance.

Glaxo Wellcome has 15 years of experience with conducting postmarketing pregnancy registries for more than 7 medicines in 6 therapeutic areas. We are pleased to have the opportunity to communicate our comments on the draft guidance for industry on Establishing Pregnancy Registries. This letter is divided into two parts; the first part provides comments on policy issues and the second part provides comments on methodologic issues.

Policy Issues

We acknowledge the effort of FDA to provide draft guidance on establishment of pregnancy registries. This methodology is not widely understood and it has not been as widely used as other more common approaches in clinical drug development. Therefore, appropriate guidance should be useful in promoting a wider understanding of such registries and greater uniformity in approach to registries.

However, the guidance document for industry seems to be unclear on the following issues regarding objectives and definitions:

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1. What is the scientific objective of the study methodology under discussion?
With respect to the scientific objective of a pregnancy registry, it is not clear whether FDA's view is that historical registries have demonstrated their value primarily in detection of a new unknown or specific safety signal during pregnancy or quantification of the frequency of observation of a known or hypothesized adverse event during pregnancy. Clarification of this or other scientific objectives (with examples from previous registries) are essential to this guidance.

2. What is the regulatory objective of the study methodology under discussion, if any?
The draft guidance should encourage FDA to notify the sponsor as early as possible in situations where FDA's scientists believe that a pregnancy registry may be warranted for a specific drug product. Such notification would typically occur after the results of reproductive toxicology studies, mutagenicity studies, and Phase II clinical studies are available for review. This schedule would allow sufficient time for discussion with the sponsor and, as appropriate, sufficient time for adequate preparation to design and open a registry, if warranted.

We encourage FDA **to** work with a sponsor to review all available data on a new compound as development progresses so that a registry would only be considered based on:

a. the weight of evidence suggesting substantial risk to pregnancy outcomes based on nonclinical reproductive toxicology studies and clinical data; and
b. a product that is intended to be used commonly by women of childbearing potential for conditions associated with high morbidity and mortality.

Page 2 of the guidance states: "*[T]he Food and Drug Administration may ask the sponsor of an approvable product to provide data on the potential risks of that product in human pregnancy under a phase-4 commitment.*" This statement suggests that FDA may withhold approval of a product until the sponsor "agrees" to establish a registry. Absent exceptional circumstances, discussions between the sponsor and FDA regarding a pregnancy registry must be entirely independent of the product review and approval process.

The second bullet on page 4, describing criteria to guide the need for a pregnancy registry, is very broad and provides little guidance on specific situations where industry can expect to anticipate discussions with FDA about the need for a registry. Shouldn't the primary consideration be known or reasonably suspected risk (based on nonclinical data, pharmacological class, etc.)?

3. Is there a standard definition of a pregnancy registry?
With respect to a standard definition of pregnancy registry, the current draft guidance does not provide one. It does seem clear that two key features of a registry are that it must be prospective in nature and it must include active collection of data of women exposed to a specific medication. The companion "draft guidance for reviewers" makes an attempt at differentiating between any observational epidemiologic study and a registry, and although

that description is not entirely clear, we recommend that a definition be stated here if a standard methodology is intended.

4. Given the broad array of objectives described in the guidelines, is it appropriate to recommend a single method or study design?

It is difficult to design a study that meets the objective of detecting any possible excess risk in all possible pregnancy-related outcomes. How large must the study population be? How long should the study last? What if the "unknown" risk of a product is cognitive impairment or developmental delay in children that doesn't manifest for several years? Infertility in the offspring? To date pregnancy registries have been largely used to detect previously unknown safety signals about the frequency of birth defects. We recommend that this draft guidance should focus solely on the potential utility of pregnancy registries for assessing suspected risks or specific adverse pregnancy outcomes based on the sum total of scientific information available. Further discussion of this point is elaborated below in the section on "Methodologic Considerations."

5. What is FDA's guidance on registry information materials?

Page 7 of FDA's guidance indicates that registry announcements and text in promotional materials should be discussed with the Review Division and DDMAC/APLS prior to implementation, and that subsequent changes be cleared with the Agency.

a. Does this refer to all mentions of the registry? At a minimum, announcements merely designed to inform physicians of the existence of a registry should not require Agency preclearance.
b. The Agency's position to implement a preclearance requirement likely exceeds FDA's authority. Rather, a sponsor must only satisfy applicable regulatory requirements and submit materials with a Form FDA 2253, as appropriate. Promotional materials are typically time-sensitive and have a defined commercial purpose. Any delay in the ability to use promotional materials while FDA reviews information about a registry will be unacceptable in the vast majority of circumstances. FDA should consider developing a standardized statement for registry announcements that sponsors could use that would not be subject to a preclearance requirement.

6. Which are the most appropriate regulations for reporting of Pregnancy Registry results?

Pages 13-14 -The last paragraph on page 13 states that adverse events identified by pregnancy registries are considered to be spontaneous reports. We believe that prospectively reported events ascertained through follow-up by the pregnancy registry are not spontaneous reports. They are collected during active recruitment of the patient into the registry, and thus should be considered solicited reports, as outlined in FDA's "*Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drugs and Licensed Biological Products: Clarification of What to Report*", August 1997, pages 3-4. Under this 1997 guidance, solicited reports are to be reported to FDA as information obtained from a postmarketing study, and only submitted to FDA if they involve serious, unexpected events which are related to the drug.

Because registries provide a systematic review of the frequency of birth defects in an exposed population, we feel that a periodic summary of findings should constitute the sole safety reporting requirement for prospectively reported pregnancy outcomes. Obviously if a strong safety signal emerges between planned periodic summaries, a discussion would be held between sponsor and FDA.

Methodologic Considerations

1. Is it appropriate to recommend a single methodology?

The draft guidance for industry states very strongly that it is preferred to enroll exposed pregnancies through patients. The document states this explicitly on page 8, and goes on to describe registries as if this is the accepted or recommended method. As mentioned above, enrolling through patients has regulatory, ethical, and resource implications for the sponsor, as well methodologic implications. We strongly recommend that no one study design be recommended for pregnancy registries. The study design and approach should depend on the scientific objectives of the study, which in turn will depend on the patient population, the known nonclinical data regarding the medication, and the amount of use in pregnant women. Glaxo Wellcome has extensive experience in managing pregnancy registries and in sponsoring external pregnancy registries. We would welcome the opportunity to have a dialogue with the FDA about methodologic and operational challenges in running such registries.

Rather than recommending a specific method and stating very explicitly what should be done in Section B (starting **on** page 7), this guidance document would be more helpful if it reviewed the strengths and weaknesses of various approaches. This is done quite successfully in the companion Draft Guidance for Reviewers on "Evaluation of Human Pregnancy Outcome Data".

2. More specific methodologic comments follow:

- Page 2: The Draft Guidance states that such registries could identify and **quantify long-term effects** such as delayed development, and other neurological impairments (also mentioned on page 11). Achievement of such objectives requires long-term follow-up, and are likely to involve subsequent large loss to follow-up. In addition, precise instruments are generally needed for outcome ascertainment. These issues may make the registry setting inappropriate for these outcomes.

- Page 3: The Draft Guidance states that **an expected time frame** for completion should be specified. In our experience, this is extremely difficult to predict. This will depend on registration rates and on the sample size which meets the statistical power consistent with the study objective. Therefore, rather than specifying the time frame, we recommend that the sample size be specified and a rationale for this be provided. It may also be useful to prepare a decision algorithm for discontinuing a registry due to slow registration.

- Page 4: The Draft Guidance states: "*Pregnancy risk information, particularly* ***comparative information,*** *is critical for products indicated for medical conditions that are caused or exacerbated by pregnancy . .*" Across-study comparisons for several medicines should be viewed very cautiously. Confounding by indication and impact of varying study designs with different objectives could produce considerable differences in results for medicines under study. Confounding by indication could be especially important when comparing outcomes for exposures to new medicines and old ones.

- Page 5: The Draft Guidance states that the **first 5 years of marketing** are the most successful for registry "recruitment". This statement is based on experience with spontaneously reported adverse events. The truth of such a statement is likely to depend on the disease area. In fact, because of the medicine's "newness", the first several years may involve very slow registration as the drug is less likely to be used in pregnancy compared to older medicines until clinicians become comfortable with the medication, In addition, clinicians are more likely to be unaware of the registry during this initial time period.

- Page 5 mentions that registries should make every effort to enroll a heterogeneous patient population in order to assess risk factors for a specific outcome within the studied population. This is certainly appropriate, but may not be very realistic. Obtaining adequate enrollment for making definitive conclusions from the total sample size can take years, and the sample **size** will be inadequate for assessing risk within subgroups.

- Page 6: FDA's Draft Guidance states that the background section of the protocol should be "*understandable to a nonspecialist health care provider.*" The intent of this statement is unclear. Typically, most health care providers do not wish to read the details of a protocol. They are usually looking for the results and interpretation. We agree that the protocol should be complete and well written, but the intent of the above statement in the guidance is not stated.

- Page 7 states that the characteristics and size of the patient population should be estimated. For most new drugs, this may be difficult to estimate. In fact, on page 15 of the Draft Guidance, it is stated that "*It will be impossible under most circumstances to ascertain the total population of women exposed to a product during pregnancy.*" What is the intent of this recommendation on page 7? If it is to compare the enrolled population to the possible exposed population, this should be stated.

- Page 8: The Draft Guidance states that pregnancies enrolled after any prenatal testing are usually considered retrospective. In fact, it is difficult to obtain enrollment before prenatal testing on a consistent basis. It would certainly be best to enroll all pregnancies this early, but in fact close to half of enrolled pregnancies may be enrolled after prenatal testing. When the sample size **is** adequate, one can test whether enrollment after prenatal test results were known had biased the enrollment of pregnancies. Until the sample size is high enough, it may not be feasible to disaggregate those reported before

and after any prenatal testing, and the review of the data can be accomplished by considering possible biases inherent in this approach.

- Enrollment after prenatal testing is likely to be the most important source of selection bias in any voluntary enrollment pregnancy registry. On page 15, referral bias is mentioned as a significant source of **selection bias.** It is conceivable that health care providers might enroll more high risk or low risk patients, but this has not been documented. However, it seems likely that the impact of this source of bias would be minimal if women are enrolled prior to prenatal testing. In addition, this document strongly recommends enrollment through patients, rather than through health care providers. However, it is clear that patients can and do self select. It is largely well-educated empowered women who enroll (as mentioned in the document), while less advantaged (and possibly higher risk) populations tend to avoid contact with registries. Patients may be afraid to enroll for a number of reasons, including language skills, fear of the medical system, and preference to remain anonymous to a study.

- Page 12 cites the March of Dimes (1996) as the source of information that minor malformations occur in 14% to 22% of births, while the table on page 5 of the Draft Guidance for Reviewers states that minor malformations occur in 5% of live births. A similar discordance occurs on page 12 of this Draft Guidance document on pregnancy registries versus the text on page 7 of the Draft Guidance for Reviewers.

- Pages 10- 11: Overall, this document suggests that any and all pregnancy-related outcomes, including maternal adverse events, can and should be studied through pregnancy registries. As with any scientific study, the approach and design should be developed around the scientific objective, and the objective of each pregnancy-related study may or may not merit a registry approach. The design will depend on the outcome of interest which in turn depends on the available scientific evidence concerning a specific medication. The design will also depend on the patient population of interest.

- Page 10: It may be useful to describe the frequency of spontaneous abortions, and a rate higher than expected in the general population would certainly suggest a signal (15%). However, formal statistical comparisons between studies are likely to be inappropriate unless adjustment for time of enrollment is performed in both studies. The reason for this is that the rate of spontaneous abortion varies signficantly within the first trimester, and studies which enroll patients at different times during the first trimester can artificially yield different spontaneous abortion rates.

- Page 11: The Draft Guidance states that the expected rate of outcomes should be described for the patient population being treated. It should also be acknowledged that frequently this information may not have been well studied in many therapeutic areas. More importantly, if treatment is standard practice during pregnancy, there may be no data available on women unexposed to a medication during pregnancy.

- Page 13 : The Draft Guidance states at the end of the analysis section that no one format of data presentation should be recommended for all studies. We agree with this statement and believe that the specific recommendations mentioned in the previous paragraphs within the data analysis section should be deleted.

- Page 14: The Draft Guidance states that maternal adverse events should be reported and that the proportion of outcomes with spontaneous abortions should be reported. Given that the outcomes of interest will vary across studies, it seems inappropriate to require the reporting of outcomes which are not outcomes of interest. They are collected during active recruitment of the patient into the registry, and thus should be considered solicited reports, as outlined in FDA's "*Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drugs and Licensed Biological Products. Clarification of What to Repor*t", August 1997, pages 3-4. Under this guidance, solicited reports are to be reported as information obtained from a postmarketing study, and only submitted to FDA if they involve serious, unexpected events which are related to the drug. FDA offers no rationale to explain why they propose that registries should not be treated like other postmarketing surveillance studies with regard to adverse experience reporting. Instead, we urge FDA to establish reasonable expedited and periodic safety reporting requirements for both prospective and retrospective reports from pregnancy registries that could be followed consistently by all sponsors.

- Page 16: The Draft Guidance states that automated record linkage studies may be performed to assess risks related to exposure during pregnancy. For new medications, it is unlikely that adequate number of exposures could be identified in this setting.

We appreciate the opportunity to comment on this important draft guidance document. We hope you find our comments constructive. Thank you.

Sincerely,

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cc: Dr. Elizabeth Andrews

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